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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
1654	

NOTIFICATION DATE	DELIVERY MODE
01/17/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/646,063	TEICHER ET AL.	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-15, 22-37* is/are pending in the application.

4a) Of the above claim(s) *24,26,27 and 34-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-15, 22-23, 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

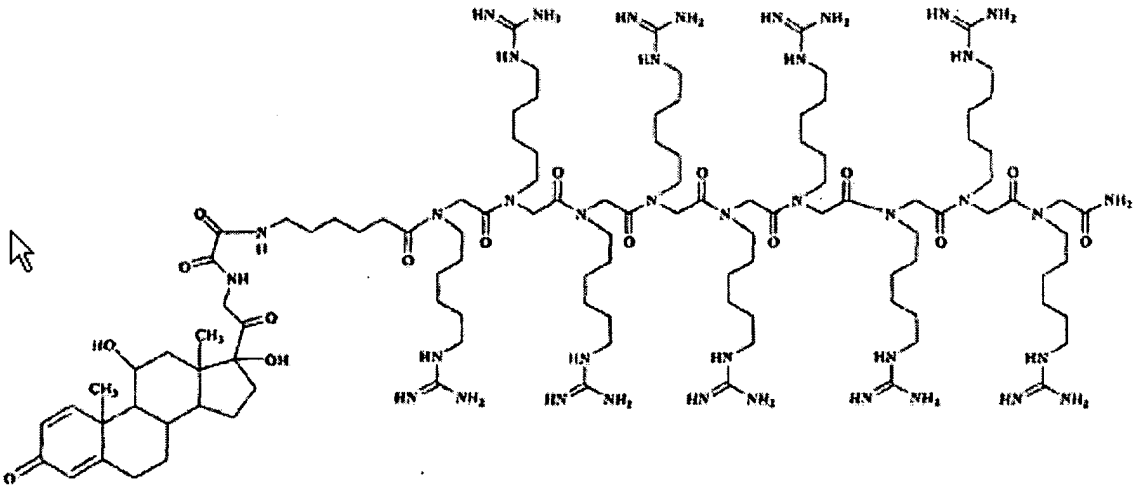
DETAILED ACTION

This Office Action is in response to the reply received on September 26, 2007.

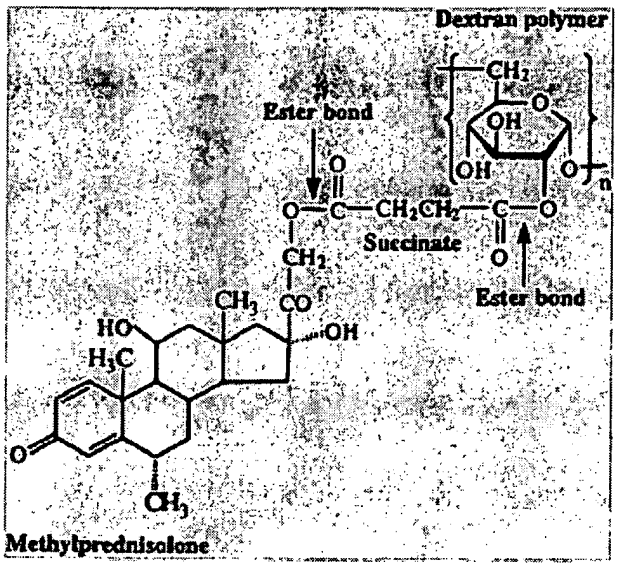
Claims 12-15, 21-37 are pending in the application. Claim 12 has been amended. Claims 33-37 are new claims.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Applicant originally elected Group II, drawn to claims 12-15 and 22-32 and new claim 33. Applicant also elected the following species: a method of treating rheumatoid arthritis with



The species (drawn to claims 12-15, 22-23, 25, 28-33) above was searched and found free of the prior art, however please note the outstanding 35 USC 112 rejections below. Examiner broadened the search and found the following species: a method of treating organ/tissue transplant rejection with



Claims 12-15, 22-23, 25, 28-33 are presented for examination on the merits as they read upon the instant species. Claims 24, 26-27 are withdrawn as not drawn to the elected and prior art species. Newly submitted claims 34-37 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the compounds are drawn to linkers that do not encompass the linkers of the presently examined species.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 34-37 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

REJECTION MAINTAINED

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-15, 22-23, 25 and 28-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include

"level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must

describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a method of treating an autoimmune or inflammatory condition in a mammal comprising administration of a corticosteroid of formula (I) attached to a group that is either a bulky group of greater than 400 Daltons or charged group of less than 400 Daltons in an amount effective to treat said condition, wherein said corticosteroid conjugate (i) has anti-inflammatory activity in vivo, (ii) has reduced activity in the central nervous system in comparison to said corticosteroid without said group and (iii) is resistant to in vivo cleavage, such that in vivo less than 10% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion. In regards to the "bulky group of greater than 400 Daltons" term, this is a very broad generic statement drawn to any chemical structure with a extremely broad molecular weight range (>400 Da), there exists a plethora of such compounds, which are not adequately described and/or represented in the examples (page 19, lines 4-22 and page 20). By the same token, the terms "charged group of less than 400 Daltons is very broad, encompassing any charged chemical composition and structure including charged polypeptides, charged polysaccharides and so forth (see, e.g., page 21, lines 1-12). The claims are drawn, to methods of using corticosteroid conjugates (including dimers, trimers and so forth) with the bulky or charged groups to treat autoimmune and inflammatory conditions such as asthma, psoriasis, eczema, organ/tissue transplant rejection, graft vs. host reactions,

Raynaud's syndrome, autoimmune thyroiditis, Grave's disease, autoimmune hemolytic anemia, autoimmune throboeytopenia purpura, mixed connective tissue disease, idiopathic Addison's disease, Sjogren's syndrome, urticaria, dermatitis, multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, uveitis, Chron's disease, ulcerative colitis, lupus, tendonitis, bursitis, adult respiratory distress syndrome, shock, oxygen toxicity, glomerulonephritis, vasculitis, reactive arthritis, necrotizing enterocolitis, Goodpasture's syndrome, hypersensitivity pneumonitis, glomerulonephritis, encephalomyelitis and meningitis. A mere statement that such compounds would be desirable for treatment of a host of diseases does not sufficiently provide ample written description pages describing the full breadth of the corticosteroids-bulky group and corticosteroids-charged group conjugates and specifically of the biological activity required to treat a host of diseases as instantly claimed. The specification does provide examples of what qualify as compounds of the claimed invention (see, e.g, disclosure, pages 29-36, Examples 3-8), however, these are limited to a few examples such as a polyguanidine peptoid derivative of prednisolone (Example 3), a hyaluronic acid conjugate of triamcinolone (Example 5), an mPEG conjugate of Budesonide (Example 6), a beclomethasone dimer (Example 7). As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 1 is a broad generic with respect all possible compounds encompassed by the claims. The possible structural variations within the method are limitless to any class of bulky group or charged group conjugated with the claimed corticosteroid. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when

accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the bulky groups and charged groups disclosed in a few examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide examples of methods of treating administrating conjugates of a representative number of corticosteroid conjugates encompassed by the instant claims to treat all the instantly claimed illnesses. The written description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Applicant's arguments

As amended, claims 12 and dependent claims 13-15 and 22-33 are limited to corticosteroid conjugates in which the corticosteroid is a compound of formula I attached to a charged or bulky group via a linker described by formula III. As noted above, the bulky or charged group is selected to modify the pharmacokinetic profile such that the corticosteroid conjugate has reduced CNS activity in comparison to its

parent corticosteroid. The specification provides clear and adequate instructions with respect to the selection of a group that provides the mere bulk or charge (see, e.g., the specification from page 19, line 4, to page 21, line 12). Applicant asserts that the structural limitations now incorporated into claim 12 are sufficient to provide one of skill in the art a written description of the claimed genus.

With respect to the use of the corticosteroid conjugates of the invention, Applicants note that these compounds are derived from parent corticosteroids which are already known to be useful for the treatment of autoimmune and inflammatory conditions (Exhibits A, B, C, D).

The prior art provides significant teaching regarding the use of corticosteroids, compounds belonging to the same structural and functional class as the corticosteroid conjugates used in the claimed methods. Applicants submit that, given the teaching of the specification and the level of skill known in the art at the time the present application was filed, one skilled in the art could instantly recognize that the Applicant was in possession of how to use the compounds recited in the claimed methods and throughout the full scope of the claims.

Response to Arguments

Applicant's arguments have been carefully considered by Examiner and deemed persuasive regarding the structure of the corticosteroid, which has now been much more specifically defined. However, Applicant's arguments are not deemed persuasive with respect to the attached bulky groups of <u>any molecular composition</u> having

molecular weight greater than 500, 500, 700, 800, 900 or 1000 daltons. Please note there is no upper limit for the bulky groups and bulky groups that are charged. With respect to the charged groups with 2, 3, 4, 5, 6, 7, 8, 9, 10 or more negatively charged moieties, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more positively charged moieties, these are not adequately described within the disclosure except for mentioning some charged moieties (carboxylate, phosphodiester, phosphoramide, borate, phosphate, phosphonate, phosphonate ester, sulfonate, sulfate, thiolate, phenolate, ammonium, amidinium, guanidium, quaternary ammonium, and imidazolium moieties) and bulky groups (poly-arginine, poly lysine, poly-aspartic acid, poly-glutamic acid or poly-histidine, hyaluronic acid. The disclosure presents working examples with guanidine and hyaluronic acid. With regards to applicant's exhibits A-D, Examiner has carefully considered them but not deemed them persuasive with respect to the instantly claimed very broad genus of 'autoimmune or inflammatory condition' which is not expressly defined in the disclosure, and encompasses any kind of autoimmune disease, such as HIV and/or any inflammatory disease including, e.g., obesity.

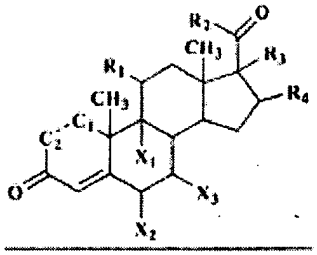
REJECTION MAINTAINED

Claim Rejections - 35 USC § 102

Claims 12-13, 15, 22-23 and 28-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (J Pharm Sci, 2001).

Zhang et al. teach a method of treating for therapeutic purposes a mammal suffering from an autoimmune disease or inflammatory condition (organ/tissue

transplantation rejection, page 2078, column 1, lines 1-3; page 2085, column 2, lines 33-52; page 2086, first paragraph), said method comprising administering to said mammal (page 2080, column 1, lines 1-20; page 2085, column 2, lines 33-52; page 2086, first paragraph) a corticosteroid attached via a linker to a group that is a bulky group of greater than 400 daltons (i.e., Dextran-70, 70,000 Da page 2079, column 2, lines 9-12, Scheme 1) in an amount effective to treat said condition, said corticosteroid conjugate (i) having anti-inflammatory activity in vivo, (ii) having reduced activity in the central nervous system in comparison to said corticosteroid without said group, and (iii) being resistant to in vivo cleavage, such that in vivo less than 10% of the administered corticosteroid conjugate is cleave, separating said corticosteroid from said group, prior to excretion (see entire document, e.g., abstract and column 1, paragraph 1, page 2079, Scheme I, page 2079 and pages 2085-2086), wherein said corticosteroid is described by formula (I):



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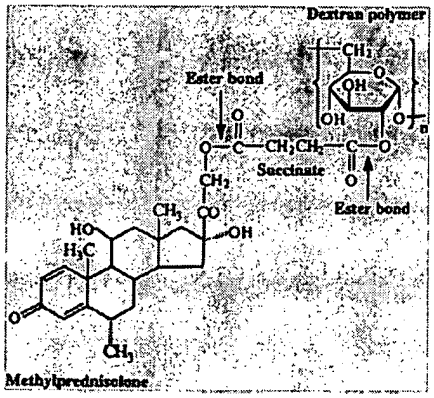


Prior art conjugate (ZHANG et al):

:

wherein the bond between C_1 and C_2 is a double bond; X_1 represents -H; X_2 represents CH_3, X_3 represents H; R_1 represents -OH; R_2 represents CH_2-O-G^1; R^3 is OH, R^4 is H (see 6α-methylprednisolone, page 2079, column 2, lines 9-16, Scheme 1), G^1 is a bond between said corticosteroid and said linker, wherein said linker is described by formula (III):

$$G^1\text{-}(Z^1)_o\text{-}(Y^1)_u\text{-}(Z^2)_s\text{-}(R_{10})\text{-}(Z^3)_t\text{-}(Y^2)_y\text{-}(Z^4)_p\text{-}G_2 \qquad \textbf{III}$$

wherein G^1 is a bond between said corticosteroid and said linker; G^2 is a bond between said linker and said bulky group; Z^1 is not present (o is zero); Y^1 is carbonyl (C=O), u is 1; Z^2 is not present (s is zero); R_{10} is C_2 alkyl (CH_2-CH_2); Y_2 is carbonyl (C=O), y is 1; Z_4 is O, p is 1, G_2 is a bond between said linker and said bulky group. The limitation of claim 13: --wherein the condition is organ/tissue transplant rejection—is taught, e.g., in page 2078, lines 1-3. The limitation of claim 15: --wherein said corticosteroid conjugate is administered by intravenous, intraperitoneal, subcutaneous,

ocular, topical, nasal or intramuscular administration—is taught, e.g., in page 2080, column 1, lines 8-10. See also Fig.1.

Please note that the limitations of claim 12: --(i) having anti-inflammatory activity in vivo, (ii) having reduced activity in the central nervous system in comparison to said corticosteroid without said group, and (iii) being resistant to in vivo cleavage, *such* that *in vivo* less than 10% of the administered corticosteroid conjugate is cleave, separating said corticosteroid from said group, prior to excretion--, the limitation of claim 22: -- wherein said corticosteroid conjugate comprises a corticosteroid attached to a bulky group and said bulky group comprises a naturally occurring polymer—or a synthetic polymer-- are inherent to the compound taught by Zhang et al. since it anticipates each and all structural limitations of the base claim. The limitation of claim 23: --wherein said bulky group comprises a polysaccharide—is taught in page 2079, column 2, lines 9-12, Scheme 1. The limitation of claim 28 : --wherein said corticosteroid conjugate comprises a corticosteroid attached to a bulky group and said bulky group comprises a corticosteroid--, the limitation of claim 29, --wherein said corticosteroid conjugate comprises a corticosteroid attached to a bulky group of greater than 600 daltons-- and the limitation of claim 30: --wherein said corticosteroid conjugate comprises a corticosteroid attached to a bulky group of greater than 800 daltons-- are taught, e.g., in page 2079, column 2, lines 9-12, Scheme 1. As above, the limitations of claim 31 : -- wherein said corticosteroid conjugate is resistant to in vivo cleavage, such that in vivo less than 5% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion--, and of claim 32: -- wherein said

corticosteroid conjugate is resistant to in vivo cleavage, such that in vivo less than 2% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion—are inherent to the compound taught by Zhang et al. since it anticipates each and all structural limitations of the base claim. Therefore, the reference is deemed to anticipate the instant claims above.

Applicant's arguments

Claim 12 has been amended to remove the wherein clause preceding limitations (i), (ii) and (iii). As amended, claim 12 and dependent claims 13-15 and 22-33, are limited to corticosteroid conjugates (i) having anti-inflammatory activity in vivo, (ii) having reduced activity in the central nervous system in comparison to said corticosteroid without said group, and (iii) being resistant to in vivo cleavage, such that in vivo less than 10% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion. For reasons of record, limitations (i), (ii) and (iii) distinguish Zhang, which describes a prodrug that is cleaved in vivo, from the corticosteroid conjugates of the invention.

Response to Arguments

Applicant's arguments have been carefully considered by Examiner, but have not been deemed persuasive for the reasons set forth above and because Zhang et al. teach that the conjugate is indeed resistant to *in vivo* cleavage, e.g., in page 2081, column 2, lines 6-12. Further, the limitation --such that *in vivo* less than 10% of the

administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion-- is not limiting, since it is only drawn to an example of the types of "resistance to *in vivo* cleavage" that the conjugates may have.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

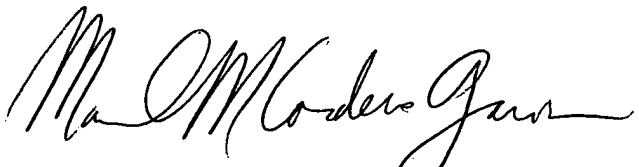
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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